APPLICANTS: Ward *et al.*
SERIAL NO: 10/719,370

DOCKET NO: PTS-0070US.P1 (ISIS.038CP1)

REMARKS

Claims 1, 3-8, 22-25, 33, 37-44, 119, 120 and 122-124 were pending. Upon entry of this Amendment, claims 1, 6-8, 22-25, 33, 37, 44, 119, 120 and 122-126 will be pending. Claims 1, 6-8, 22-25, 33, 37, 44, 119, 120 and 122 are amended, claims 3-5 and 38-43 are canceled and new claims 125 and 126 are submitted herein.

Claim 1 is amended to incorporate the limitations of claim 5 (wherein the compound is an antisense oligonucleotide); limit the oligonucleotides to 15 to 30 nucleobases in length; and replace "an 8-nucleobase portion" with "8 consecutive nucleobases." Support for these amendments can be found, for example, at pages 27-28 of the specification. Claim 1 is further amended to remove the unnecessary functional limitation of specific hybridization with HIF1α. Claims 6-8, 22-25, 33, 37, 44 and 120 are amended to replace "compound" with "antisense oligonucleotide" for proper antecedent basis. Claims 6-8 are further amended to depend from claim 1 and for clarity. Claims 22-25 are further amended to replace "having" with "comprising" for clarity. Claim 33 is further amended to specify inhibition of HIF1α expression *in vitro*. Claim 199 is rewritten as an independent claim. Claim 122 is amended to replace "compound" with "antisense oligonucleotide" for proper antecedent basis. Basis for new claims 125 and 126 can be found throughout the specification and claims as originally filed, such as, for example, at pages 39, 51-52, 83-84 and 88-89 of the specification. No new matter has been added to the claims.

The specification is amended to correct minor typographical and spelling errors. The specification also is amended to remove reference to the priority claim submitted in a Preliminary Amendment May 27, 2004, which was filed in conjunction with a Petition to accept an unintentionally delayed claim for priority. In accordance with the Examiner's determination of priority, the instant application no longer claims priority to U.S. Serial No. 10/304,126, filed November 23, 2002. No new matter has been added to the specification.

The claim amendments and cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action. Applicant reserves the right to file subsequent applications claiming the canceled subject matter.

EXAMINER INTERVIEW AND CORRECTION OF CLAIM NUMBERS

Applicants thank Examiner Zara for the telephone interview in which the claim numbers indicated as rejected under 35 U.S.C. 112, first paragraph (the enablement rejection), were corrected. The Examiner confirmed that only claims 33 and 38-43 are under rejection for allegedly lacking enablement. Applicants later discovered that the claims listed as being rejected under 35 U.S.C. 112, first paragraph for written description, also appeared to be incorrect as claims previously canceled were included in the rejection. Applicants assume the Examiner intended to reject only claims 1, 3-8, 22-25, 33, 37-44 and 122-124 and prepared a response accordingly.

PRIORITY

The Office Action notes U.S. Application Serial No. 10/304,126, to which the instant application currently claims priority, does not provide support for the claimed subject matter because the priority document does not disclose SEQ ID NO: 446. Applicants concur that the instant application, filed November 21, 2003, provides the first disclosure of SEQ ID NO: 446. Accordingly, Applicants have amended the specification to delete the reference to the priority claims submitted in the Preliminary Amendment and Petition filed May 27, 2004.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1, 3-8, 22-25, 33, 37-44 and 122-124 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written descriptive support in the application. The Office Action states the genus of nucleic acids claimed encompasses a myriad of structures and the specification and claims do not adequately teach a representative number of species for the broad genus claimed. Specifically, the application does not disclose any sequences with less than 100% identity to the complement of SEQ ID NO: 133. Thus, the Office Action concludes the claimed subject matter was not described in the specification in such a way as to convey to one of skill in the relevant art that Applicants had possession of the claimed subject matter at the time of filing. Applicants respectfully traverse this rejection.

Pending Claims

Claims 3-5 and 38-43 are canceled herein, rendering the rejection moot as it pertains to

these claims. Claim 1 is directed to an antisense oligonucleotide 15 to 30 nucleobases in length targeted to a nucleic acid molecule encoding HIF1α (SEQ ID NO: 133), wherein said compound comprises at least 8 consecutive nucleobases of SEQ ID NO: 446. Claims 4-8 and 22-25 further limit the antisense oligonucleotide of claim 1 to a DNA oligonucleotide; an RNA oligonucleotide; a chimeric oligonucleotide; and an antisense oligonucleotide comprising at least one modified internucleoside linkage, such as a phosphorothioate, sugar moiety, such as 2'-O-methoxyethyl, or nucleobase, such as 5-methylcytosine. Claim 33 is directed to a method of inhibiting expression of HIF1α using the antisense oligonucleotide of claim 1. Claims 37 and 44 are directed to a kit or assay device comprising the antisense oligonucleotide of claim 1 and a composition comprising the antisense oligonucleotide of claim 1, respectively.

Claim 122 is directed to an antisense oligonucleotide 16, 17, 18, 19, 20, 21, 22, 23 or 24 nucleobases in length targeted to a nucleic acid molecule encoding HIF1-alpha (SEQ ID NO: 133), wherein said antisense oligonucleotide has at least 80% identity with SEQ ID NO: 446. Dependent claims 123 and 124 are directed to an antisense oligonucleotide 18, 19, 20, 21 or 22 nucleobases in length having at least 90% identity with SEQ ID NO: 446, and an antisense oligonucleotide 19, 20 or 21 nucleobases in length having at least 95% identity with SEQ ID NO: 446, respectively.

The Pending Claims are Adequately Supported by the Written Description

The test for sufficiency of support under the written description requirement was provided by the Court in *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991), which stated, "Although [the applicant] does not have to describe exactly the subject matter claimed...the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (citations omitted). The decision rendered in *Vas-Cath, Inc. v. Mahurkar* was affirmed in *Falkner v. Inglis*, No. 05-1324 (US Court of Appeals for the Federal Circuit, May 26, 2006), which concluded that:

> (1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of the known structure.

The decision by the Federal Circuit in *Falkner v. Inglis* is in accordance with prior case

law, including *Lizard Tech, Inc. v. Earth Resource Mapping, PTY, Inc.* 424 F.3d 1336, 1345 (Fed. Cir. 2005) and *Union Oil Co. v. Atlantic Richfield Co.* 208 F.3d 989, 997 (Fed. Cir. 2000), which concluded, "A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language."

While the instant application does not provide a listing of each and every sequence encompassed by the pending claims, Applicants are still in compliance with the written description requirement. As noted above, there is no requirement to provide explicit examples covering the full scope of the claims. Applicants have provided a number of explicit examples of antisense oligonucleotides falling within the genus claimed and have provided sufficient disclosure to describe the remaining oligonucleotides of the claimed genus, such that one of ordinary skill in the art would recognize Applicants to be in possession of the claimed invention.

Whether the written description requirement is met is a question of fact, determined on a case-by-case basis. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil V. Atlantic Richfield Co.* Given the "nature" of antisense technology, one of ordinary skill in the art need only be provided with a target sequence against which to design antisense oligonucleotides, a description of how to make and use the antisense oligonucleotides, length limitations, chemical modifications, acceptable ranges of complementary, and an exemplary antisense oligonucleotide (e.g., SEQ ID NO: 446) in order to conclude that Applicants were in possession of the invention as instantly claimed. The instant specification thoroughly discloses each of these aspects. The description provided by the instant application imparts a wide breadth of knowledge on antisense compounds, including antisense oligonucleotides, targeted to HIF1α (SEQ ID NO: 133). For example, the specification describes antisense compounds specifically hybridizable with a target nucleic acid, antisense compounds complementary to the target, including compounds that need not be 100% complementary to the target nucleic acid. Preferred compounds are described as at least 70%, at least 90% and at least 95% complementary to the target (see, for example, pages 22-24 of the specification). The specification further describes antisense compounds having a variety of lengths, including 8 to 80, 12 to 50 and 15 to 30 nucleobases (see page 27 of the specification).

The antisense oligonucleotides are further described as including at least 8 consecutive nucleobases of an exemplified sequence (such as instantly claimed SEQ ID NO: 446; see pages 27-28 of the specification). The specification further describes how antisense compounds are targeted to a nucleic acid sequence (see, for example, pages 28-29 of the specification) and provides numerous oligonucleotide modifications (see pages 39-49 of the specification). Examples 1-4 provide a description for synthesis of oligonucleotides, while Examples 7 and 8 describe the synthesis and analysis of antisense compounds using a 96-well plate format. In addition, specific antisense oligonucleotides targeted to SEQ ID NO: 133 (Genbank Accession No. U29165.1) are exemplified in Examples 15, 17 and 29.

In particular, Table 13 on page 115 of the specification shows eight oligonucleotides that comprise at least 8 consecutive nucleobases of SEQ ID NO: 446 (see SEQ ID NOs: 443, 444, 233, 141, 445, 447, 448 and 450). Four of the oligonucleotides comprising at least 8 consecutive nucleobases of SEQ ID NO: 446 (SEQ ID NOs: 443, 444, 233 and 450) have 2, 3 or 4 mismatched nucleotides relative to the HIF1α target sequence (SEQ ID NO: 133). Furthermore, Table 3, beginning on page 89 of the specification, provides four oligonucleotides comprising at least 8 consecutive nucleobases of SEQ ID NO: 446 (see SEQ ID NOs: 140-143). Thus, the specification provides many specific examples of sequences falling within the claimed genus (i.e. antisense oligonucleotides targeted to HIF1α (SEQ ID NO: 133) comprising at least 8 consecutive nucleobases of SEQ ID NO: 446), including oligonucleotides which are not 100% complementary to the HIF1α target sequence.

Taken together, the instant application provides a thorough description of the antisense oligonucleotides currently claimed and provides a number of specific sequences falling within the scope of the claims. As noted above, Applicants need not provide each and every sequence of the antisense oligonucleotides covered by the instant claims. In fact, "the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification" (*Falkner v. Inglis*) and is discouraged by the Patent Office as it only serves to increase application page numbers and overload sequence databases.

Furthermore, as detailed in the MPEP, the initial burden of proof in establishing whether the claims are supported by an adequate written description falls upon the Examiner. "The description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to

the contrary has been presented by the examiner to rebut the presumption" (MPEP 2163.04 and *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)). The Examiner has not provided any evidence to show that one of skill in the art, given the disclosure (described in detail above), would not recognize Applicants to be in possession of the claimed compounds and methods.

Conclusion

In accordance with the written description requirement, the instant application provides a more than adequate description of that which is claimed, such that one of ordinary skill in the art would recognize Applicants to be in possession of the claimed invention. Therefore, Applicants respectfully submit the claims are in condition for allowance.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 33 and 38-43 are rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. The Office Action argues that the specification, while being enabling for a method of inhibiting the expression of HIF1α (SEQ ID NO: 133) in vitro using antisense oligonucleotides, and for inhibiting expression of SEQ ID NO: 133 in vivo comprising administering antisense oligonucleotides of SEQ ID NO: 139, 141 or 193, the specification does not reasonably provide enablement for methods of inhibiting expression of HIF1α in vivo or methods of treating a disease or condition associated with HIF1α.

Without agreeing with the Examiner's position in the Office Action, and solely to advance prosecution, claim 33 is amended herein to specify inhibition "in a cell in vitro" and claims 38-43 are canceled. Applicants respectfully submit the rejection is now moot and request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

REJECTIONS UNDER 35 U.S.C. §102/103

Claims 1, 4-7, 37 and 44 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as allegedly being obvious over Kung *et al.* (EP 0147819). The Office Action alleges Kung *et al.* teach compositions comprising a pharmaceutically acceptable diluent and an antisense oligonucleotide 12-50 nucleobases in

length, comprising at least an 8-nucleobase portion of SEQ ID NO: 446 and specifically hybridizes with SEQ ID NO: 133. The Office Action concludes the burden of establishing whether the oligonucleotide of Kung *et al.* has the function of specifically binding to SEQ ID NO: 133 falls to Applicants. Applicants respectfully traverse this rejection.

The rejected claims are directed to antisense oligonucleotides 15 to 30 nucleobases in length which are targeted to HIF1α (SEQ ID NO: 113) and comprise at least an 8-nucleobase portion of SEQ ID NO: 446. The instant specification clearly describes "8-nucleobase portion" as a stretch of at least 8 consecutive nucleobases of one of the illustrated preferred compounds (see pages 27-28 and 32-33 of the specification). However, for additional clarity, Applicants have amended claim 1 herein to replace "an 8-nucleobase portion" with "8 consecutive nucleobases." In contrast to the instant claims, the sequence disclosed by Kung *et al.* comprises, at best, a 5-nucleobase portion of SEQ ID NO: 446. Furthermore, the sequence of Kung *et al.* is only 12 nucleotides in length, which falls outside the scope of the claims as amended herein.

Kung *et al.* do not teach or suggest each and every limitation of claims, therefore the cited reference does not anticipate, nor render obvious, the pending claims. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(b) and/or §103.

Claims 1, 4-7, 37 and 44 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as allegedly being obvious over Baird *et al.* (U.S. 6,958,240). The Office Action alleges Baird *et al.* teach compositions comprising a pharmaceutically acceptable diluent and an antisense oligonucleotide 12-50 nucleobases in length, comprising at least an 8-nucleobase portion of SEQ ID NO: 446 and specifically hybridizes with SEQ ID NO: 133. The Office Action concludes the burden of establishing whether the oligonucleotide of Baird *et al.* has the function of specifically binding to SEQ ID NO: 133 falls to Applicants. Applicants respectfully traverse this rejection.

As noted above, the pending claims are limited to antisense oligonucleotides 15 to 30 nucleobases in length. In contrast, Baird *et al.* disclose a compound which is 13 nucleotides in length. Since Baird *et al.* do not teach or suggest every limitation of the claims, the reference does not anticipate or render obvious the pending claims.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C.

§102(e) and/or §103.

REJECTION UNDER 35 U.S.C. §102(e)

Claims 1, 3-8, 22-25, 33, 37 and 44 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Usman *et al.* (WO 2005/035759). The Office Action states Usman *et al.* teach the inhibition of HIF1α (SEQ ID NO: 133) in vitro comprising administration of an antisense oligonucleotide 12-50 nucleobases in length, comprising at least an 8-nucleobase portion of SEQ ID NO: 446, and specifically hybridizable with SEQ ID NO: 133. The Office Action further states Usman *et al.* describe 5-methylcytosine modified residues, phosphorothioate internucleoside linkages, 2'-O-methoxyethyl modifications and pharmaceutically acceptable diluents. Applicants respectfully traverse this rejection.

Applicants provide herewith a Declaration of inventor Dr. Eric Marcusson under 37 C.F.R. § 1.131 to establish Applicants' date of invention in this country prior to August 20, 2003, which is the earliest date to which the Usman *et al.* reference claims priority. This Declaration demonstrates that Dr. Eric Marcusson conceived of and reduced to practice the claimed invention in the United States prior to August 20, 2003. Dr. Marcusson further declares that his notebook entry regarding this invention, included herewith as "Exhibit A", demonstrates the design of ISIS 330449, an antisense oligonucleotide with the sequence of SEQ ID NO: 446. Dr. Marcusson declares that he conceived of and possessed antisense oligonucleotides targeted to HIF1α, including a number of antisense oligonucleotides comprising at least an 8-nucleobase portion of SEQ ID NO: 446, as claimed in the instant application. Since Applicants' date of invention in this country was prior to August 20, 2003, the earliest possible priority date of the Usman *et al.* reference, the Usman *et al.* reference should not be considered prior art under 35 U.S.C. § 102(e).

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(e).

ALLOWABLE SUBJECT MATTER

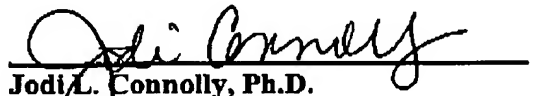
The Examiner indicated that SEQ ID NO: 446 is free of the prior art. In addition, the Office Action Summary notes claims 119 and 120 are objected to; however, objections to these claims are not mentioned in the Office Action. Applicants assume claims 119 and 120 were

objected to as being dependent upon a rejected base claim. Claim 119 is rewritten as an independent claim herein, rendering the objection moot. Furthermore, Applicants submit claim 1, from which claim 120 depends, is in condition for allowance. Thus, claims 119 and 120 are in condition for allowance.

It is believed that no fee is due with this response. However, if a fee is due, the Commissioner is hereby entitled to charge the fee to Deposit Account 50-0252, referencing the above named application.

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Withdrawal of the pending rejections and reconsideration of the claims is respectfully requested. If the Examiner believes that there are any remaining issues in the case that could be resolved by a telephonic interview, the Examiner is encouraged to contact the Agent for Applicant listed below to discuss any outstanding matters.

Respectfully submitted,



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